Psychopharmacology Institute

Asenapine (SAPHRIS) Pharmacokinetics

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Source: Drug labeling information submitted to the Food and Drug Administration (FDA), updated by the National Library of Medicine (NLM).

Following a single 5-mg dose of SAPHRIS, the mean Cmax was approximately 4 ng/mL and was observed at a mean tmax of 1 hour. Elimination of asenapine is primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). Following an initial more rapid distribution phase, the mean terminal half-life is approximately 24 hrs. With multiple-dose twice-daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Absorption

Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg is 35%. Increasing the dose from 5 mg to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The absolute bioavailability of asenapine when swallowed is low (<2% with an oral tablet formulation).

The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration.

Distribution

Asenapine is rapidly distributed and has a large volume of distribution (approximately 20 - 25 L/kg), indicating extensive extravascular distribution. Asenapine is highly bound (95%) to plasma proteins, including albumin and α1-acid glycoprotein.

Metabolism and Elimination

Direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2) are the primary metabolic pathways for asenapine.
Asenapine is a high clearance drug with a clearance after intravenous administration of 52 L/h. In this circumstance, hepatic clearance is influenced primarily by changes in liver blood flow rather than by changes in the intrinsic clearance, i.e., the metabolizing enzymatic activity. Following an initial more rapid distribution phase, the terminal half life of asenapine is approximately 24 hours. Steady-state concentrations of asenapine are reached within 3 days of twice daily dosing.

After administration of a single dose of [14C]-labeled asenapine, about 90% of the dose was recovered; approximately 50% was recovered in urine, and 40% recovered in feces. About 50% of the circulating species in plasma have been identified. The predominant species was asenapine N+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. SAPHRIS activity is primarily due to the parent drug.

In vitro studies indicate that asenapine is a substrate for UGT1A4, CYP1A2 and to a lesser extent CYP3A4 and CYP2D6. Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Coadministration of asenapine with known inhibitors, inducers or substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies.

Smoking

A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, had no effect on the clearance of asenapine in smokers. In a crossover study in which 24 healthy male subjects (who were smokers) were administered a single 5-mg sublingual dose, concomitant smoking had no effect on the pharmacokinetics of asenapine.

Food

A crossover study in 26 healthy male subjects was performed to evaluate the effect of food on the pharmacokinetics of a single 5-mg dose of asenapine. Consumption of food immediately prior to sublingual administration decreased asenapine exposure by 20%; consumption of food 4 hours after sublingual administration decreased asenapine exposure by about 10%. These effects are probably due to increased hepatic blood flow.

In clinical trials establishing the efficacy and safety of SAPHRIS, patients were instructed to avoid eating for 10 minutes following sublingual dosing. There were no other restrictions with regard to the timing of meals in these trials

Water

In clinical trials establishing the efficacy and safety of SAPHRIS, patients were instructed to avoid drinking for 10 minutes following sublingual dosing. The effect of water administration following 10-mg sublingual SAPHRIS dosing was studied at different time points of 2, 5, 10, and 30 minutes in 15 healthy male subjects. The exposure of

asenapine following administration of water 10 minutes after sublingual dosing was equivalent to that when water was administered 30 minutes after dosing. Reduced exposure to asenapine was observed following water administration at 2 minutes (19% decrease) and 5 minutes (10% decrease)

Special Populations

Hepatic Impairment

The effect of decreased hepatic function on the pharmacokinetics of asenapine, administered as a single 5-mg sublingual dose, was studied in 30 subjects (8 each in those with normal hepatic function and Child-Pugh A and B groups, and 6 in the Child-Pugh C group). In subjects with mild or moderate hepatic impairment (Child-Pugh A or B), asenapine exposure was 12% higher than that in subjects with normal hepatic function, indicating that dosage adjustment is not required for these subjects. In subjects with severe hepatic impairment, asenapine exposures were on average 7 times higher than the exposures of those in subjects with normal hepatic function. Thus, SAPHRIS is not recommended in patients with severe hepatic impairment (Child-Pugh C)

Renal Impairment

The effect of decreased renal function on the pharmacokinetics of asenapine was studied in subjects with mildly (creatinine clearance (CrCl) 51 to 80 mL/min; N=8), moderately (CrCl 30 to 50 mL/min; N=8), and severely (CrCl less than 30 mL/min but not on dialysis; N=8) impaired renal function and compared to normal subjects (CrCl greater than 80 mL/min; N=8). The exposure of asenapine following a single dose of 5 mg was similar among subjects with varying degrees of renal impairment and subjects with normal renal function. Dosage adjustment based upon degree of renal impairment is not required. The effect of renal function on the excretion of other metabolites and the effect of dialysis on the pharmacokinetics of asenapine has not been studied

Geriatric Patients

In elderly patients (N=96) with psychosis (65-85 years of age), asenapine exposure (AUC) was on average 40% higher compared to younger adult patients. No dosage adjustment is necessary. In a population pharmacokinetic analysis, a decrease in clearance with increasing age was observed, implying a 30% higher exposure in elderly as compared to adult patients